Elimination of Racial Differences in Invasive Pneumococcal Disease in Young Children After Introduction of the Conjugate Pneumococcal Vaccine

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Background: Racial differences in the epidemiology of invasive pneumococcal disease (IPD) have been widely recognized, but the impact of conjugate pneumococcal vaccine (PCV) introduction in 2000 on these differences has not been extensively studied.

Methods: IPD episodes in 5 Tennessee counties from January 1995 through December 2002 were collected prospectively using the Centers for Disease Control and Prevention's Active Bacterial Core Surveillance system (ABCs). Trained nurses collected clinical data, and antibiotic susceptibility testing was performed on available isolates.

Results: Before vaccine licensure, IPD rates were highest in children younger than 2 years and in blacks. The disparity in IPD rates between blacks and whites younger than 2 years of age substantially diminished after PCV introduction. In 1999, the IPD rate in black children younger than 2 years was 340.2 per 100,000, representing 176.5 more events per 100,000 than in white children ($P < 0.001$). In 2002, this rate had decreased 83% to 57.4 per 100,000, similar to the rate in white children (39.6 per 100,000; $P = 0.31$). Before vaccine licensure, a higher percentage of isolates from whites were antibiotic-nonsusceptible. In 2002, the proportion of antibiotic-nonsusceptible pneumococcal isolates was similar in whites and blacks of all ages for the first time during the study period ($P > 0.05$ for separate comparisons of penicillin, cephalosporin and erythromycin nonsusceptibility). These changes occurred despite a lower PCV vaccination coverage in Tennessee in blacks than in whites (31.2% versus 47.6%).

Conclusions: With conjugate pneumococcal vaccine introduction in Tennessee, racial differences in the incidence rates of IPD have largely been eliminated, particularly in young children.

Key Words: *Streptococcus pneumoniae,* racial disparity, epidemiology, antibiotic resistance, pneumococcal conjugate vaccine

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The risk of disease caused by *Streptococcus pneumoniae*, a leading cause of acute otitis media, pneumonia and bacterial meningitis, is increased in the setting of certain intrinsic host and extrinsic environmental factors, such as underlying immunodeficiency, cigarette smoking and chronic lung disease.[1] Race also influences one's risk of developing pneumococcal disease; blacks, Native Alaskans and Native Americans are all at increased risk of invasive pneumococcal disease (IPD) when compared with whites.[2–5]

In addition, pneumococcal disease caused by strains nonsusceptible to many commonly used antibiotics has become a growing concern, particularly in Tennessee, where in some regions >70% of pneumococcal isolates are penicillin-nonsusceptible.[6,7] In contrast to their lower risk of developing invasive pneumococcal disease, the proportion of pneumococcal disease by antibiotic-nonsusceptible strains has historically been higher in whites than in other racial groups.[7–9] Higher antibiotic prescription rates in whites than in blacks with the subsequent selection pressure for reduced antibiotic susceptibility likely play a major role in this difference.[7,10]

In 2000, a 7-valent conjugate polysaccharide vaccine (PCV) containing pneumococcal serotypes commonly associated with invasive and antibiotic-nonsusceptible strains of *S. pneumoniae* was approved for routine use in healthy children younger than 2 years of age and older children with

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certain high risk conditions.[11] In only 2 years after vaccine introduction, initial surveillance reports demonstrated a sizeable reduction in the incidence of IPD, a finding most pronounced in children younger than 2 years of age.[12] Although this initial surveillance also noted a larger decline in incidence rates in young black children compared with whites,[12] the impact of PCV on racial differences in the epidemiology of IPD, and antibiotic-nonsusceptible disease in particular, has not been fully examined. To determine the effect of PCV introduction on racial differences in IPD in Tennessee, we reviewed comprehensive surveillance data on invasive pneumococcal disease from 1995 to 2002.

MATERIALS AND METHODS

Ascertainment of Episodes of Invasive Pneumococcal Disease. Surveillance for invasive disease by *S. pneumoniae* has been performed in Tennessee as a part of the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance (ABCs) program of the Emerging Infections Program Network.[13] Since January 1, 1995, Tennessee surveillance for invasive pneumococcal infections has included 5 urban counties encompassing the state's 4 major metropolitan centers (Memphis, Nashville, Knoxville and Chattanooga), covering a total population of 2,283,929 (40% of the state's population).[14] Case finding was active and laboratory-based, utilizing hospital microbiology and reference laboratories that process sterile site specimens for surveillance area residents. IPD was defined as the isolation of *S. pneumoniae* from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone or joint fluid).[13] In the event that *S. pneumoniae* was isolated concurrently from multiple sites from one subject, the overall episode was counted as a single case of invasive disease. The study interval extended from January 1, 1995 through December 31, 2002.

Data Abstraction. For each episode of invasive disease identified, information on demographics (age, race, gender), comorbid conditions, source of pneumococcal isolate (blood, cerebrospinal fluid, other normally sterile site or body fluid) and outcome of illness was abstracted from clinical records by trained ABCs program nurses using standardized definitions and abstraction criteria.[13] The procedures and definitions used for data abstraction did not change during the study period. An audit of the surveillance process in Tennessee revealed incomplete reporting rates from 1 institution in Shelby County from 1995 to 1999. Through a recent (2002–2003) audit of this institution's laboratory databases, previously unreported episodes of IPD were identified, and case report forms were completed based on clinical records and added to the main surveillance database.

Antibiotic Susceptibility Data. Available pneumococcal isolates from IPD cases were sent to the reference laboratory at the University of Texas Health Science Center at San Antonio for susceptibility testing. Serotyping was also performed for available isolates identified after 1997, as described previously.[7,13] Antibiotic susceptibility data for the additional Shelby County episodes were based on local clinical laboratory testing. Nonsusceptibility was defined based on National Committee for Clinical Laboratory Standards definitions as the presence of intermediate or high level resistance to the specific antimicrobial tested by broth microdilution (eg, penicillin mean inhibitory concentration (MIC) $\geq$ 0.1 μg/ml, cefotaxime MIC $\geq$ 1 μg/ml and erythromycin MIC $\geq$ 0.5μg/ml). PCV serotypes were defined as those serotypes found in the 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F and 23F), PCV-related serotypes were defined as serotypes within the same serogroup as the vaccine types (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A and 23B), and nonvaccine serotypes were defined as serotypes not included or related to the PCV.

Statistical Analysis. Rates of invasive disease were expressed using annual population data based upon Census 2000 statistics (for year 2000) and annual population estimates (for years 1995–1999 and 2001–2002).[14] Because of low representation of other racial and ethnic groups, analysis of racial differences in disease rates and in the proportion of nonsusceptible isolates was limited to persons of white and black races. Trends in incidence rates and the proportion of resistant isolates during the study period were analyzed with the Cochran-Armitage test for trend. Results were examined separately in children younger than 2 years of age, the primary target for vaccination, and in all persons age 2 years and older. Comparisons between annual rates in specific demographic groups and the rate differences between demographic groups were compared based on Pearson's χ^2 test for proportions. Analyses were conducted using STATA version 7.0 (Stata Corp., College Station, TX) and SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

During the 7 study years, 4319 episodes of IPD were detected in the 5 surveillance counties of Tennessee. The mean age of the study subjects was 41.7 $\pm$ 30.1 years (mean $\pm$ SD) with 20% (n = 865) of episodes occurring in children younger than age 2 years. Of the total, 55% (2361) were male, 54% (2311) were white and 44% (1887) were black. The remaining episodes occurred in Native Americans (2 episodes, 0.05%), Asians (15, 0.35%), other (11, 0.25%) or unknown races (93, 2.3%). Hispanics represented only 1.2% (53) of the study population. County distribution of episodes closely mirrored the population distribution.

Racial Differences in the Incidence Rate of Invasive Pneumococcal Disease. Whites had a lower incidence of invasive disease compared with blacks in the years before PCV licensure (Fig. 1). In children younger than 2 years, the

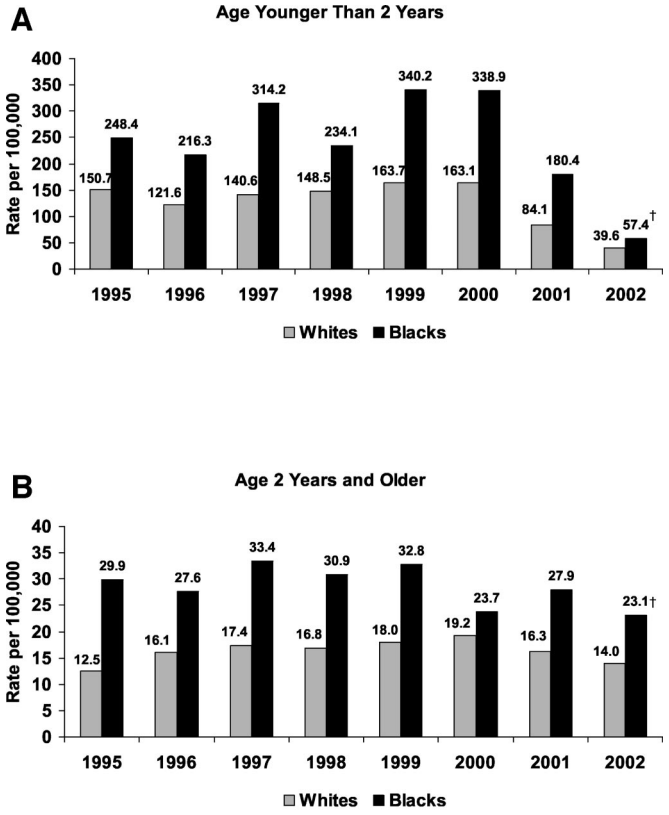

FIGURE 1. Annual incidence rates of invasive pneumococcal disease in Tennessee by race and age strata. PCV was introduced in 2000. A, Age younger than 2 years. † indicates trend from 1999 to 2002. $P < 0.001$ for both blacks and whites. B, age 2 years and older. † indicates trend from 1999 to 2002. $P < 0.01$ for both blacks and whites.

rate of IPD in both whites and blacks peaked in 1999, with a sharp decline in rates in both races after the introduction of the PCV in 2000. Among whites, there was a 75.8% decrease to 39.6 episodes per 100,000 persons in 2002; among blacks there was an 83.1% decrease to 57.4 per 100,000 ($P < 0.001$ for both trends). In 2002, the incidence rate of disease in blacks younger than 2 years was no longer significantly different than that in whites ($P = 0.31$). In addition, the difference in the incidence of IPD in blacks compared with whites in this age group had strongly declined from 176.5 to 17.8 cases per 100,000.

In persons 2 years and older, rates of IPD declined in both whites and blacks after vaccine introduction. In whites, incidence rates declined by 22.2% from 1999 to 2002 to 14.0 per 100,000; among blacks, there was a 29.6% decrease from 1999 to 2002 to 23.1 per 100,000 ($P < 0.01$ for both trends). The gap in incidence of IPD between blacks and whites also narrowed considerably, from 14.8 episodes per 100,000 in 1999 to 9.1 per 100,000 in 2002. However, in this age group of persons age 2 years and older, rates in blacks were still significantly greater than whites ($P < 0.001$).

Racial Differences in the Epidemiology of Antibiotic-Nonsusceptible Pneumococcal Disease. Antimicrobial susceptibility data were available for 73.4% of isolates during the surveillance period. Testing was not performed on all isolates because of lack of recovery from the initial source laboratory and reduced isolate viability after storage and shipment. Slightly more isolates from blacks were sent for susceptibility testing than whites (75.9% versus 71.2%) during the surveillance period, whereas susceptibility testing was performed on similar proportions of isolates in persons younger than 2 years (73.6%) and age 2 years and older (73.1%). The proportion of antibiotic-nonsusceptible pneumococcal isolates causing invasive disease was substantially higher in whites than blacks before PCV licensure (Fig. 2). After vaccine introduction in 2000, the proportion of antibiotic-nonsusceptible isolates declined significantly in isolates

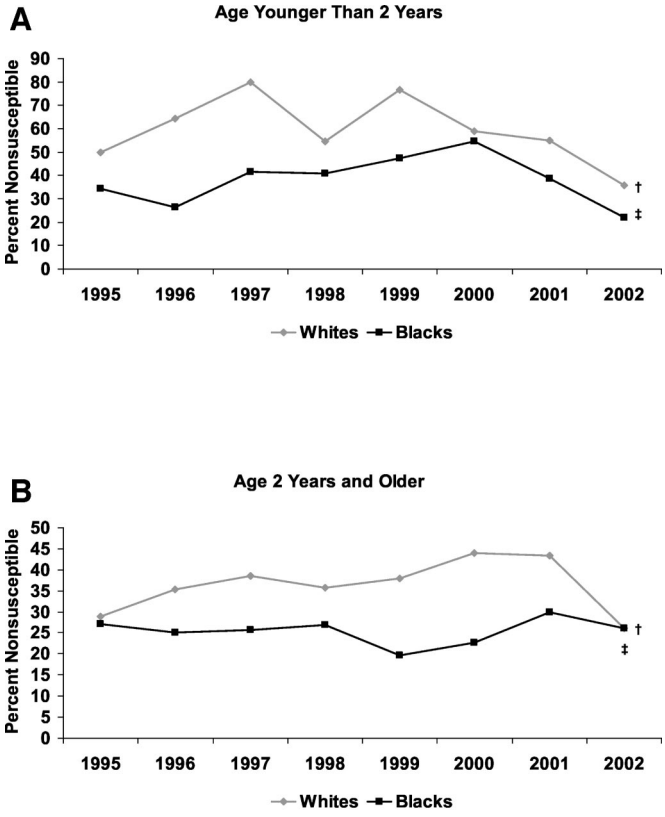

FIGURE 2. Proportion of invasive pneumococcal isolates nonsusceptible to penicillin, by year and race. PCV was introduced in 2000. Gray line indicates white race; black line, black race. A, Age younger than 2 years. † indicates trend in whites from 1999 to 2002; $P < 0.01$. ‡ indicates trend in blacks from 2000 to 2002; $P < 0.05$. B, age 2 years and older. † indicates trend in whites from 1999 to 2002; $P < 0.001$. ‡ indicates trend in blacks from 2000 to 2002; P not significant.

from both white and black children younger than 2 years. In isolates from whites, the proportion nonsusceptible to penicillin declined from 76.7% in 1999 to 35.7% in 2002 ($P < 0.01$ for trend). Similarly in blacks, the proportion of isolates that was penicillin-nonsusceptible decreased from 54.6% in 2000 to 22.2% in 2002 ($P = 0.03$ for trend). Similar significant declines in cephalosporin- and erythromycin-nonsusceptible isolates also occurred in both whites and blacks during these periods (data not shown; $P < 0.05$). In 2002, the proportions of penicillin-nonsusceptible isolates from whites and blacks were equivalent ($P = 0.49$).

In persons age 2 years and older, nonsusceptibility to penicillin rose steadily among isolates from whites from 1995 to 2001 (increased from 29% to 43.3% penicillin-nonsusceptible in 2001; $P < 0.01$ for trend). Likewise cephalosporin and erythromycin nonsusceptibility also increased among isolates from whites in this age group during this time (data not shown; $P < 0.001$). In 2002, the proportion of isolates nonsusceptible to penicillin, cephalosporin or erythromycin significantly declined in whites age 2 years and older (eg, 26.2% of isolates from whites were penicillin-nonsusceptible, $P < 0.01$ for comparison to 2001). In black persons age 2 years and older, however, the proportion of isolates that was antibiotic-nonsusceptible did not decline from 1995 to 2002. Specifically penicillin and cephalosporin nonsusceptibility remained stable during the study period (eg, 27.2 and 26.2% of isolates in 1995 and 2002, respectively, were penicillin-nonsusceptible; $P = 0.99$ for trend), whereas the proportion of erythromycin-nonsusceptible isolates increased during this time (from 7.8% to 15.9%, $P = 0.046$ for trend). Nonetheless in 2002, just 2 years after the licensure of the conjugate vaccine, the difference in the proportion of antibiotic-nonsusceptible isolates between whites and blacks age 2 years and older had been eliminated ($P > 0.05$ for individual comparisons of penicillin, cephalosporin and erythromycin nonsusceptibility).

Serotype Analysis. Serotype analysis was performed on 73.8% (n = 1990) of all IPD isolates from cases that occurred after 1997, the year serotyping was first available through the ABCs program. Overall the rate of invasive disease caused by PCV serotypes significantly decreased in blacks and whites younger than 2 years after PCV introduction in 2002 (Figs. 3 and 4). PCV serotype IPD incidence also significantly declined in whites 2 years and older (1999, 7.2 cases/100,000; 2002, 3.6 cases/100,000; $P < 0.001$). PCV serotype disease declined in blacks 2 years and older from 11.7 cases/100,000 in 1999 to 8.5 cases/100,000 in 2000, but this change did not reach statistical significance ($P = 0.06$). There were no significant changes in IPD rates due to nonvaccine serotypes in either racial group. In the combined analysis of whites and blacks 2 years and older, PCV-related serotypes significantly increased from 1.3 cases/100,000 in 1999 to 2.3 cases/100,000 in 2002 ($P < 0.05$). We previously reported an increase in non-PCV-specific serotypes (including PCV-related serotypes) in all persons age 2 years and older from 1999 to 2002.[15]

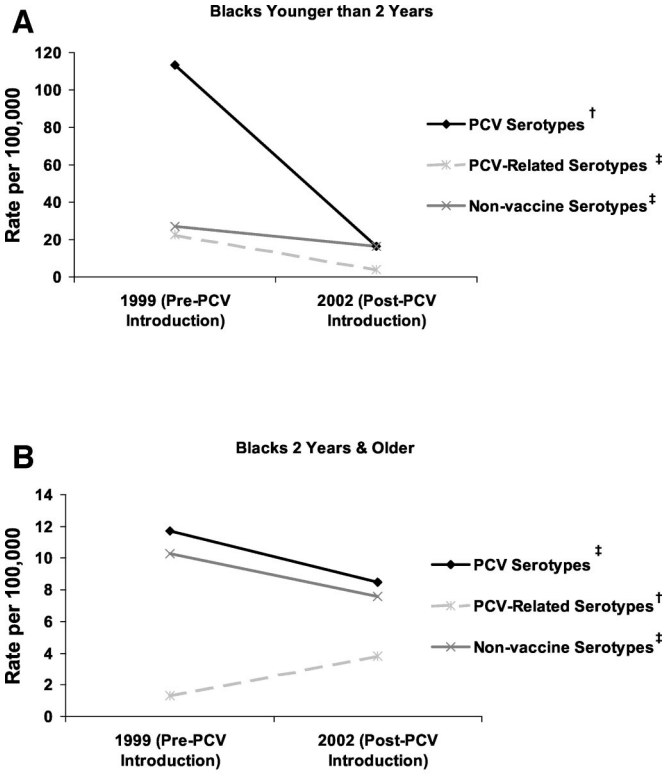

FIGURE 3. Serotype-specific incidence rates of invasive pneumococcal disease in blacks, by relationship to the PCV introduction. A, Age younger than 2 years. † indicates $P < 0.001$ for comparison between 1999 and 2002 rates; ‡, *P* not significant for comparison between 1999 and 2002 rates. B, Age 2 years and older. † indicates $P < 0.01$ for comparison between 1999 and 2002 rates. ‡ indicates *P* not significant for comparison between 1999 and 2002 rates.

DISCUSSION

Although black race has been associated with increased risk for IPD,[2,3,7,16] whites have a higher prevalence of invasive disease caused by antibiotic-resistant pneumococcal strains,[2,7,9,10] which may be attributed to increased antibiotic exposure in whites compared with that in other races.[10] Enhanced susceptibility to pneumococcal infection, as well as reduced access to preventive and therapeutic care for blacks[17] and increased antibiotic exposure in whites,[10] may contribute to the varying epidemiology of pneumococcal disease, although racial differences have remained after controlling for such factors.[10]

Targeting serotypes related to both invasive and antibiotic-nonsusceptible pneumococcal disease, the 7-valent PCV was expected to strongly reduce the burden of IPD in

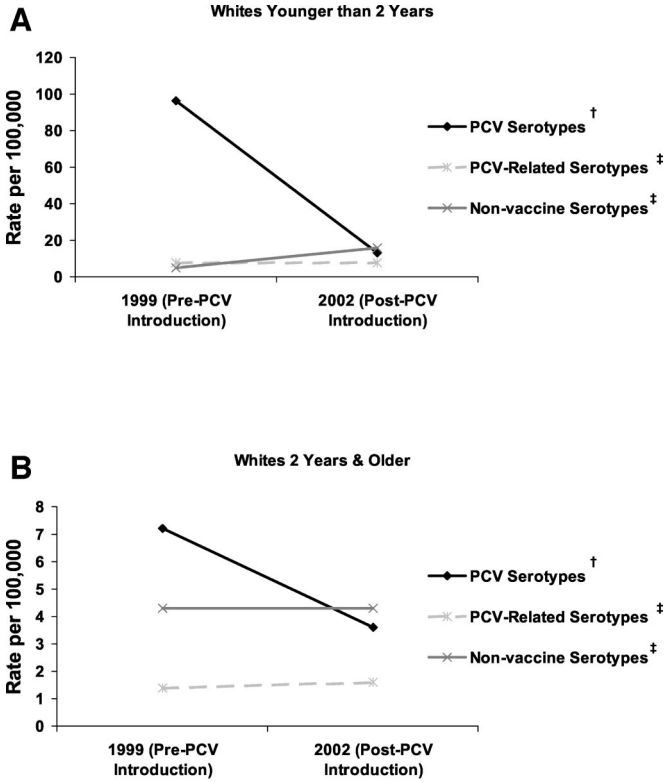

FIGURE 4. Serotype-specific incidence rates of invasive pneumococcal disease in whites, by relationship to the PCV. A, Age younger than 2 years. † indicates $P < 0.001$ for comparison between 1999 and 2002 rates; ‡, P not significant for comparison between 1999 and 2002 rates. B, Age 2 years and older. † indicates $P < 0.001$ for comparison between 1999 and 2002 rates; ‡, P not significant for comparison between 1999 and 2002 rates.

young children. An initial review of multistate surveillance data found that in just 2 years after vaccine introduction, IPD incidence had declined by 69% in children younger than 2 years. A smaller yet significant decrease was noted in adults.[12] Disease rates attributable to penicillin-nonsusceptible strains also diminished by 35% from 1999 to 2001, suggesting an impact by the PCV on invasive disease due to resistant strains.[12]

Although this initial analysis of PCV's impact also noted a larger decline in incidence rates of IPD in black children younger than 2 years than in white children,[12] the effect of the PCV on racial differences in IPD incidence and antibiotic-resistant disease has not been extensively examined. Since the introduction of the PCV in Tennessee, differences in the epidemiology of IPD between whites and blacks have substantially decreased, and racial differences in both the rate of invasive disease (traditionally higher in nonwhites) and the proportion of antibiotic-nonsusceptible isolates (traditionally higher in whites) have been eliminated in children younger than 2 years of age. In children 2 years and older, including adults, differences in the proportion of antibiotic-nonsusceptible isolates were largely eliminated by 2002, even though the incidence rate of disease in this age group remained significantly higher in blacks. In addition, serotype-specific incidence rates indicate a sizeable decline in IPD caused by PCV-specific serotypes, reinforcing the hypothesis that PCV introduction accounted for the reduction in IPD. These findings highlight the significant benefit of widespread administration of an effective vaccine.

Some potential limitations to our investigation may exist. The declining trends in antibiotic-nonsusceptible disease may be influenced by other factors, such as improved antibiotic stewardship and subsequently reduced antibiotic exposure. In an examination of National Ambulatory Medical Care Survey data, nationwide trends in antibiotic prescribing for children younger than 5 years peaked in 1995 with a subsequent decline through 1999.[18] Similarly antibiotic prescription rates in children younger than 15 years from 4 of the Tennessee ABCs surveillance counties decreased during a 3-year period of study from May 1996 through April 1999.[19] These data suggest that the antibiotic selection pressure decreased during the study period and that any impact from decreased antibiotic prescribing would likely have occurred earlier in the course of our surveillance. Because reductions in antibiotic resistance may lag behind changes in antibiotic prescription practices,[20] however, reduced antibiotic prescribing cannot be completely eliminated as a factor influencing the epidemiology of antibiotic-nonsusceptible disease in Tennessee.

The changing epidemiology of antibiotic-nonsusceptible IPD may also be attributed to racial differences in antibiotic prescription rates. In the early 1990s, national antibiotic prescription rates were significantly higher in white children than in black children (rate ratio in blacks versus whites of 2.1 in 1993–1994). However, by 1998 the difference in prescription rates, although still significantly higher in whites (rate ratio, 1.2), had declined markedly.[18] If this trend continued during the study period, the effect of small differences in antibiotic prescribing patterns on antibiotic resistance was likely small if not entirely absent.

Detailed information on racial differences in PCV delivery in the surveillance area is not available. Immunization audits found completion rates of all recommended childhood immunizations in Tennessee children age 2 years and younger from 1995 to 1999 to be 84% in blacks and 87% in whites ($P = 0.02$).[21] Although excluding vaccination with the PCV, which had not yet been licensed for use, these data provide reassurance that racial differences in overall vaccine administration in Tennessee were likely minor during our study period. In 2002, when PCV coverage was included for the first time in the CDC's National Immunization Survey, vaccination coverage of children age 19–35 months in Ten-

nessee mirrored national percentages (Tennessee, 41.8% received PCV; nationwide, 40.8%); however, the coverage in Tennessee was higher in white children (47.6%) than in black children (31.2%) in the target age group.[22] Even with this gap in vaccine delivery, the incidence rate of IPD in black children declined as strongly as the rate in white children.

The generalizability of our surveillance population, encompassing predominately urban regions of a single state, may also be limited; however, our findings are supported by recently presented data from other surveillance areas in the United States.[23] In addition, the epidemiology of IPD in Tennessee has consistently mirrored national trends.[7]

These data provide encouraging support of the impact of the PCV on racial differences in IPD. Since the introduction of the PCV in Tennessee, racial differences in IPD incidence, especially that of antibiotic-resistant disease, have largely been eliminated in young children, with a similar trend in all other ages. These alterations in the epidemiology of IPD are exciting and suggest that the introduction of a safe and effective vaccine for widespread use, while producing a greater impact in those at higher risk of disease, also provides a benefit to lower risk populations.

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